Stem Cell Therapies: California Dreamin'?

Ready or not, stem cells are a step closer to the clinic, thanks to ~$230 million awarded by CIRM to 14 California-based research groups to develop stem cell-based therapies within 4 years. But, as Kris Novak reports, some of these projects are closer to therapeutic reality than others.

The California Institute for Regenerative Medicine (CIRM) recently granted ~$230 million in Disease Team Research Awards to get stem cell-based therapies into the clinic within 4 years (http://www.cirm.ca.gov). Up to ~$20 million will go to each of 14 California-based interdisciplinary research groups, with the first funding checks to be sent out next month. The expectation is that within 4 years each group will submit an Investigational New Drug (IND) application to the US Food and Drug Administration (FDA) for a phase I clinical trial. To receive the funding, the research teams are required to include basic scientists and clinicians from academia and industry, with the goal of getting test agents rapidly into clinical trials and addressing clinical issues early in the research process. CIRM's President, Alan Trounson, estimates that 75% of the projects funded will result in IND applications to the FDA within the 4 year funding period. "I am impressed with these teams—some have already had pre-application meetings with the FDA," says Trounson. He emphasizes that all of the Disease Teams include researchers that have been through the IND application process.

The CIRM-funded projects propose to develop new stem cell therapies to treat 11 diseases including AIDS, diabetes, sickle-cell anemia, amyotrophic lateral sclerosis (ALS), ischemic heart disease, several different types of cancer, stroke, macular degeneration, and the rare genetic skin disease dystrophic epidermolysis bullosa. "We were open to all stem cell approaches and wanted to include as many diseases as possible, especially those with no cures…we wanted to see creative uses of stem cells and encouraged investigators to aim higher and bite off bigger chunks than in most grant applications," says Bettina Steffen, Science Officer at CIRM. The review committees "considered any role of the stem cell as part of the actual therapeutic or even as part of a screening platform to identify drugs," she adds.

Some of the more advanced projects are variations on current clinical practices. Two separate groups—one led by Irving Chen at UCLA (awarded almost $20 million) and one by John Zaia (awarded $14.5 million) from the City of Hope Medical Center in Duarte, CA—received funding to develop autologous hematopoietic stem cell transplantation therapies for patients with AIDS. These projects aim to reduce expression of the HIV coreceptor CCR5 on hematopoietic stem cells from AIDS patients, each by a different mechanism. After transplantation of the modified hematopoietic stem cells back into the patient, the stem cells differentiate into lymphocytes that should be resistant to infection by HIV. Many AIDS patients already receive bone marrow transplants for AIDS-related lymphoma, and loss of HIV replication has been reported in an AIDS patient with leukemia who received bone marrow stem cells expressing a nonfunctional form of CCR5.

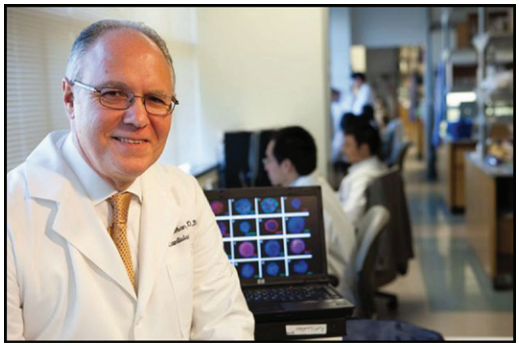

Figure 1. CIRM Grants for Stem Cell Therapies
Eduardo Marbán, director of the Cedars-Sinai Heart Institute in Los Angeles, has been awarded $5.56 million by CIRM to develop cardiac stem cells for treating heart disease. Photo courtesy of Cedars-Sinai Heart Institute.

Steffen explains that "some of the studies funded are on a more-articulated path to an IND, facilitated by past experience." The CIRM money will be used by the AIDS research teams to optimize the modification of hematopoietic stem cells. Zaia's team disrupts the CCR5 gene sequence using zinc-finger nucleases, and Chen's team plans to down-regulate CCR5 expression in hematopoietic stem cells using lentiviral vectors expressing small hairpin RNAs. "It's difficult to get funding for these types of preclinical studies," says Chen. "We will use the money to get the vector into the stem cells, select the best patient population, and investigate different means of myeloablative therapies."

One project receiving CIRM funding that Trounson predicts will result in an IND submission within 2 years is spearheaded by Eduardo Marbán of the Cedars-Sinai Heart Institute in Los Angeles (Figure 1). Marbán has been given $5.5 million to isolate and expand cardiac stem cells from patients with advanced ischemic cardiomyopathy. The goal is to inject the stem cells back into the cardiac muscle to repair the damaged tissue and form new cardiac muscle and blood vessels. Cardiac stem cells are already being tested in a phase I/II clinical trial of 13 patients, funded by the National Institutes of Health (NIH) (http://clinicaltrials.gov/ct2/show/NCT00893360). Another ~1000 patients are being treated with bone marrow-derived cells to test their effects in improving cardiac function. "These cells have a good safety protocol but marginal efficacy," says Marbán.

The CIRM funding will allow Marbán's team to compare the effects of two different types of autologous cardiac stem cells (cardiospheres and individual cardiosphere-derived cells), investi-

gate the effects of injecting the cells directly into cardiac muscle, and test stem cell efficacy in patients at more advanced stages of heart failure. "There is an absence of NIH funds to get from clever mechanistic insights to new treatments…CIRM's funding makes deliverables achievable," says Marbán.

Although the NIH provides funding for the basic research that leads to new therapeutic strategies, it provides little for the pharmacokinetic, toxicology, and scale-up experiments that are needed to prepare an IND application for the FDA. As a result, many scientists have to hand off their ideas to biotechnology or pharmaceutical companies at this stage of development. "Before the CIRM money, our options were to license our antibody or start our own biotech company," says Ravi Majeti, co-principal investigator with Irving Weissman at Stanford University; their team received ~$20 million to generate a monoclonal antibody to destroy leukemia stem cells. "We can use the CIRM funds to develop this therapeutic inside the academic arena—to pursue an optimal cure strategy [for leukemia], not just establish antibody efficacy and try to get the antibody onto the market like a drug company would do." Many recipients of CIRM funds say that the money would allow them to keep their therapeutic approach in their own lab and optimize an overall treatment strategy. "At a company, the goal is the bottom line—we want to continue to investigate the biology of this approach," says Majeti.

"The CIRM funding is a dream made in heaven," says Stanford scientist Garry Nolan, of the ~$20 million grant his multidisciplinary team was awarded to develop small-molecule drugs against cancer-initiating cells in solid tumors. The team, which includes oncologist Dennis Slamon (UCLA) and signaling researcher Tak Mak (University of Toronto), is one of only a few that can identify cancer stem cells in tumors of the brain, colon, and ovary. These investigators have developed assays to accurately test the effectiveness of drug candidates in killing cancer stem cells. Although they haven't stated what specific type of drug they plan to develop, Nolan says they plan to target novel kinases that they expect to identify in cancer-initiating cells. "I can't imagine pulling together an NIH grant to do this; it wouldn't fund something so bench-to-bedside or so high-risk," says Nolan.

Some of the Disease Team Research Awards have gone to projects that are still at very early stages of development and have large obstacles to overcome before they can be turned into clinical trial proposals. The Stanford team of Alfred Lane, Anthony Oro, and Marius Wernig has been awarded a CIRM grant of ~$12 million to derive induced pluripotent stem (iPS) cells from the skin of patients with the blistering skin disease epidermolysis bullosa. The goal is to replace the abnormal collagen VII (*COL7A1*) gene that causes this disease with the wild-type gene in the skin-derived iPS cells. Then the corrected iPS cells will be induced to differentiate into basal keratinocytes that will be used to make sheets of epidermis for grafting. This project, however, is still in its infancy. Before the researchers can even begin to think about an IND application, they must demonstrate homologous recombination at the *COL7A1* locus in iPS cells, coax the iPS cells to differentiate into keratinocytes, and then evaluate the efficacy and toxicity of the corrected keratinocytes in a human tissue model of epidermolysis bullosa—a decade-long project for most laboratories.

"We're optimistic, but we need a lot of things to go right," says Oro. "It's remarkable how fast the stem cell field is moving." Although this project is a long-shot to get to the FDA in 4 years, it is important because there are no therapeutic options for patients with epidermolysis bullosa. The reviewers of Oro's grant proposal also pointed out that discoveries made through this effort will advance the use of iPS cell-derived therapies for other disorders.

"There are a lot of challenges to some of the projects," says Trounson. "Some of the teams know that they have to clear some major hurdles within the first year; these groups have to get off to a quick start." The progress of each team will be evaluated informally each quarter and in a formal presentation each year to an established committee of independent, non-CIRM scientists. "After one year, go/no-go decisions will be made for each project—if the teams don't meet their milestones, we won't allocate any more funds to the project," warns Trounson.

CIRM has developed a tough reputation of intensive oversight for all of the projects that it funds—3 of the 73 "Scientific Excellence through Exploration and Development" projects they funded in 2007 were recently revoked because of inadequate progress. "Most academic scientists are not used to this kind of oversight," says Oro. "It's different from submitting an NIH progress report every few years—it's more like industry." Marbán emphasizes that he thinks it is healthy for grants to be held accountable in terms of deliverables. However, he says, "I hope the agency will be open to opportunities created by new discoveries—we wouldn't want to be tied to the original plan if it was based on outdated data. I am optimistic it will be an iterative process."

Nonetheless, some stem cell researchers believe that many more basic science questions should be answered before these cells can be put into patients. George Daley, Director of the Stem Cell Transplantation Program at Children's Hospital Boston, says, "outside the blood, the field of stem cell treatments is in its infancy. We are still ignorant about how products of pluripotent stem cells will behave in vivo. We're still learning about differentiation, function, and engraftment… I don't know of many cell products based on embryonic stem cells that are ready for clinical application."

Lawrence Goldstein (University of California, San Diego), co-principal investigator of a team that received a $15.6 million CIRM grant to generate astrocyte precursors from human embryonic stem cells (hESCs) to treat ALS, believes that clinical research should push forward. "We think we know what happens to these cells in vivo. They seem to integrate. Do they move to other tissues? We don't know yet. We hope that they're going to function as astrocytes in the spinal cord but it's going to take us a while to find out." Only four of the Disease Team Research

Awards were granted to groups developing hESC therapies. Research on hESCs is still in its early stages and faces many controversies and challenges. A phase I clinical trial by Geron, a California-based biotech company, to test oligodendrocyte progenitor cells derived from hESCs to treat patients with spinal cord injury was recently halted because of findings from animal studies that raised safety concerns. Goldstein admits, "This is pretty early days—we have genetic evidence that the astrocytes are good targets [for treating ALS] … but the details of all the things they're doing is not clear; it may not be clear for a while. The goal is not necessarily to know what's going on, the goal is to find a way to make these cells safe and effective and transplantable."

The pressure is on CIRM to provide new stem cell-based therapeutics for the people of California, who in 2004 voted to support Proposition 71, a ballot initiative to provide $3 billion for stem cell research. "Californians don't care if we get 100 *Cell* papers out of this research," says Trounson; "for the community to recognize our accomplishments, we need to demonstrate clinical benefits."

According to Trounson, CIRM is currently spending about $200 million/year on stem cell research, with the expectation that CIRM's funding will last at least through 2016. At that point, CIRM hopes to have sufficient therapies developed to encourage industry and venture capital firms to continue funding CIRM's stem cell research.

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